advantages and disadvantages I outlined before, and the other option was to advise our colleagues in the States that we could go for what is known as a creamer pack. A creamer pack, I don't know if you're familiar with a creamer pack commonly used to store milk, where you pour, tear the top off and tip it into the coffee, individual packs. I don't know what you call them in the States; we call them creamer packs in the UK. That package would be what's known as a unit dose pack. The top is tall and there's one dose in there, whereas the bottle is a multidose pack and during the use of that is the opportunity to remove syrup and get contamination.

If we had a creamer pack, the manufacturer could be controlled within the factory and the pack would be used once only, so there isn't the problem of the in-use contamination; take off the top, use the product and discard. So that was an option. However, the marketing requirements for the States were for a multiple-dose product, so we needed to get back to produce a formulation suitable for a bottle for multiple use.

The other consideration and option I was looking at, apart from ethanol, there are a range of other antimicrobial preservatives that I considered, bearing in mind that ethanol may have given problems stability-wise, there may have been medical objections to it, so I wanted another few shots in the locker as backups. Listed on this

page are some of the things that I was thinking of. These are handwritten notes from my own files. One is written, as chlorhexidine, C-H-L-O-R-H-E-X-I-D-I-N-E. I have two question marks against that. I, I indicated that wasn't my suggestion, somebody else said why don't you choose this. My instinctive reaction to that is, I have written here, try to kill it, done, IC toxicity. That's an example of where a possible preservative had been suggested but because it's toxic when taken by mouth it could be immediately thrown out.

At this stage I cast a very broad net, very broad net, and acted quickly to work medically to work through the possible preservatives. Some were thrown out very quickly. There is an example there. Another one is phenoxyethanol that is listed here.

THE COURT: Spell that.

A P-H-E-N-O-X-Y-E-T-H-A-N-O-L. In the, in reading the literature we discovered this one is specifically designed to kill *Pseudomonas cepacia*, which was obviously very attractive to us. It could be a winner. The question mark here on this one, it had an unknown action at the pH of 7. We didn't know how it would behave at that pH. That's a common factor in any antimicrobial preservative, the efficacy depends on the pH. Some are better at low pH, some are better at high. That really is an underlying thing for this case. The pH runs about 7 for ranitidine stability is one of the worst pHs

to get a preservative to work. It's a fairly restricted range, which is why we have a history of the problems.

So with phenoxyethanol we actually tried it and it did kill the bugs. Then a consideration there was what did it taste like? Always in this operation we're going through was what was the background, has it been used before, does it kill bugs; then we get to secondary considerations, what does it taste like. That comes back to the patient. The most important person in all of this is the patient. It's no use having a wonderfully stable product, the bugs are dead, but the patient doesn't like the taste.

So phenoxyethanol did kill the bugs. We kept it in reserve because we then found that ethanol did the job and probably phenoxyethanol could be used even today. We have found no reason for not using it.

Some preservatives I looked at, one there, it's benzalkonium chloride, B-E-N-Z-A-L-K-O-N-I-U-M, chloride, this is an example of where I was using imagination. There is no precedent for using this product by mouth, but I have worked on other products where this ingredient was used as a preservative for a product to go into the eye or into the nose, and the product delivered to the eye or the nose, some of it goes down the back of the throat into the digestive system, so there was a tenuous precedent for using benzalkonium chloride. My thought is what does it taste

like, has anybody tasted benzalkonium chloride? Does it kill the microorganism? We would need extra analytical methods for this ingredient. Would it cause, I have written here stringiness. This is another factor, another phenomenon that can occur in this type of product. The product is thickened with a cellose and the cellose with certain ingredients can decide to throw out a solution to form bits of string and gel, very inelegant.

A final consideration of benzalkonium chloride is what is the toxicology? How acceptable is it to take this material by mouth?

THE COURT: Doctor, what did you mean by extra analytical study?

THE WITNESS: In common with any ingredient we add, it will have to be analyzed as part of the specification of that product, as part of control. Because having introduced an ingredient to kill microorganisms, we needed to know at the time of manufacture is there enough in there, is there the right amount in there and also during storage is there still a sufficient level to maintain the quality of the product.

THE COURT: That would have been true about any --

THE WITNESS: It would have been true of any of them, right. We did try benzalkonium chloride and immediately got a crystalline precipitate. This is part of